Radio-frequency plasma in combination with aerosol injection for biomedical applications.

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Abstract: Radiofrequency plasma for biomedical applications generated in coaxial geometry at atmospheric pressure was investigated. The plasma was characterized by key parameters, including gas temperature and electron density. It was shown that OH rotational temperature is in agreement with the temperature estimated by Rayleigh and Raman scattering techniques. RF plasma was combined with an aerosol injection for better control of the treated skin temperature and topical drugs delivery.

Keywords: aerosol, gas temperature, emission, radiofrequency plasma

1.Introduction

The use of non-equilibrium discharges for wound healing or even its disinfection has been reported in recent literature as a promising technology [1,2]. The plasma techniques used in skin and wound healing used to be limited only to simple cutting and coagulation, but recently larger progress has been made in studies of healing chronical wounds like ulcers and plasma treatment of wounds for faster healing and/or reduction of bacteria [3]. However, the new research confirmed that the effectiveness of plasma treatment strongly correlates with the production rate of active species in the discharge. The main active species taking part in disinfection are O, O_3, H_2O_2, OH, metastables, nitrogen oxides, and UV radiation [4]. Atmospheric pressure plasmas can strongly decrease the survival rates of a wide range of bacteria and even viruses, which suggests incorporating plasma as an agent in sterilization procedures [5].

Very new unexplored field of atmospheric plasma application is the transdermal and topical molecules delivery. Transdermal molecules delivery offers an attractive non-invasive alternative to the conventional delivery methods such as oral administration and injection. The main advantage of the delivery through the skin is the possibility of molecules to enter the circulation, avoiding the metabolic processing of the delivered molecules into the liver. However, the stratum corneum acts as a limiting barrier, therefore only small lipophilic molecules have the ability to penetrate the skin at therapeutic rates by passive diffusion. Conventional transdermal delivery systems such as transdermal patches, enable controlled transdermal molecules delivery, but are applicable only to small, potent and lipophilic solutes and the transport of molecules across the skin is slow with lag times to reach steady-state fluxes in hours. Therefore, to deliver larger molecules with therapeutic levels, many clinical and physical methods were developed. Many studies were focused on so-called active strategies as sonophoresis, iontophoresis and electroporation [6,7]. At the same time plasma present a direction and a bridge between physical and chemical methods, which has not been explored.

In this work we aim at development and characterization of plasma source capable of direct drug delivery to skin with no physical damage of the skin due to very low heat flux. The plasma source is developed for a specific medical application case, namely the use of a plasma for topical molecule introduction into the skin and body. A critical case is that of chronic wounds like ulcers, which cannot be healed by conventional means or drugs are used in excessive quantities.

2.Experimental set-up and methods

Plasma device was engineered of two coaxial aligned metal electrodes separated by a gap. Powered inner electrode was made of stainless steel with inner and outer diameters of 10 mm and 12 mm, respectively. The grounded outer electrode was made of aluminum with 14 mm inner diameter. Schematic of the source and applied diagnostics is shown in Figure 1. Plasma source was powered with RF generator CESAR 136 (Advanced Energy Industries) operating at 13.56 MHz with L-type matching box. Discharge was sustained with feed gas Ar. Depending on the application gas flow was chosen to be 2 slm (standard liter per minute), 3, and 4 slm. In case of gas flow higher than 4 slm the discharge cannot be sustained in stable mode. Plasma was formed at the tip of the nozzle in an annular shape effluent in ambient air.

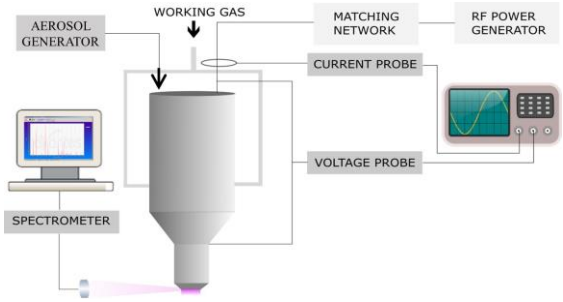

Figure 1. Schematic of the RF plasma source and applied diagnostics. Laser scattering system and fast imaging camera are not shown on the figure.

For the purpose of drug delivery the aerosol of water or ethanol with dissolved drug was applied through the center of the plasma source. Aerosol was generated by ultrasonic generator working at 80 kHz with typical droplet size of 10's of μm and solvent flow rate in the range of 0.1-10 ml/min, depending on application. Electric current and voltage of the discharge were measured with IV probe (Vigilant) and were recorded with oscilloscope (LeCroy Wavesurfer). Fast imaging with 5 ns resolution was performed with a use of Hamamatsu ICCD camera with bandpass filter centered at 750 nm. For the purpose of diagnostics, emission spectroscopy in UV/Visible range with resolution of 0.05 nm was applied coupled with laser scattering at 532 nm used for detection of Rayleigh and Raman signal of the heavy species in the discharge effluent.

3. Results and discussion

Electrical breakdown leading to ignition of RF plasma can be achieved by application of RF forward power above 100 W. At high power above 30 W the discharge starts in γ-mode, which manifests as highly localized discharge sustained by secondary emission of the electrons from hot spot localized on one of the electrodes. The γ-mode discharge can be transfer to uniform and diffuse α-mode by decreasing the RF forward power below limit of 30 W. At this power the discharge transits to α-mode filling the whole area between the electrodes. According to measurements the plasma source stable operating range is from 10 W (minimum RF power to sustain plasma) to 30 W (γ-mode transition). In the case of adding nitrogen/air to the gas flow, for emission spectroscopy purposes, α-mode was in the range of power from 13 W to 30 W. Length of the visible effluent is in the range of 2.5 - 5 mm corresponding to minimum and maximum power. It is interesting to note that increase of the gas flow rate from 2 to 4 slm has very little impact on electrical characteristics of the plasma source. However, at flow rate above 4 slm the discharge sustaining in stable regime is not possible and plasma randomly completely extinguished. Considering linear V/I characteristic of the discharge with a positive slope of 94.7 V/A the plasma operates in glow–like mode sustained by Ohmic electrons heating indicating that the main ionization processes are driven by fast electrons accelerated in oscillating RF field. Sustained RF glow discharge is characterized by constant V/I phase difference of about 88° that implies on stability of α-mode and discharge capacitive character.

Evolution of plasma constituents during a RF cycle was experimentally studied by use of fast imaging of the discharge emission presented on Figure 2.

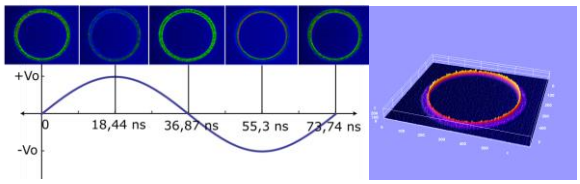

Figure 2. *Time resolved imaging of the discharge with 5ns exposure time: left) The images of Ar I emission. Time of the records is indicated in the offsets; right) 3D map of intensity for a case of 55.4 ns time frame with indication of the sheath formed near powered electrode.*

Time resolved imaging indicates formation of the sheath and development of strong intensive emission near virtual cathode. Based on energy and recombination/ionization processes analysis it has been revealed that the presence of the sheath in RF plasma allows stabilizing the discharge and generating uniform α-mode plasma without filaments or transition to γ-mode. It also play an important role in formation of low temperature afterglow. The temperature of the afterglow has been measured by 3 different methods based on emission spectroscopy, Rayleigh and Raman laser scattering.

The Rayleigh radial resolved signal presented on Figure 3 has been averaged along of the laser beam in order to determine space averaged T_g which can be directly compared with emission spectroscopy measurements. Obtained results of Rayleigh scattering as a function of gas flow rate and forward RF power are presented on Figure 3. Obtained results indicate that T_g in plasma without aerosol is in the range of 300-350±15 K, depending on applied flow and power. As presented on Figure 3, the RF power growth results in almost linear increase of gas temperature of the effluent. The maximum increase of 20 K was found for smallest flow rate of Ar gas due to less effective heat transfer at small flow. Radial averaged value of T_g measured by the Rayleigh scattering is in very good agreement with OES method based on OH(A-X) emission.

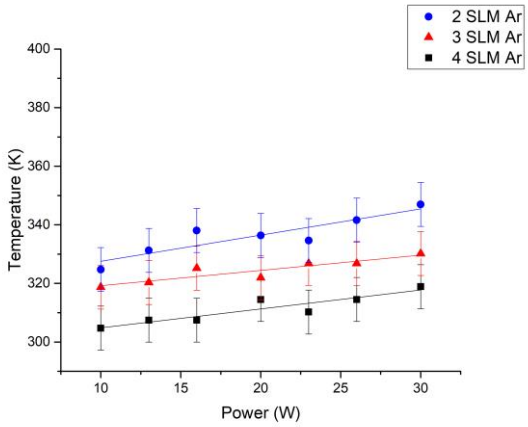

Figure 3. Radial averaged temperature vs RF power.

Considering application of develop source for enhanced drug delivery additional set of tests has been performed to study two effect:

(i) Effect of skin (or skin simulation material) in contact with effluent on gas phase temperature and thermal damage of skin

(ii) Effect of aerosol injection on thermal impact of plasma on skin surface.

Typical thermal pattern of plasma in contact with Biobrain® skin simulation material located at 2 mm distance from the nozzle is shown on figure 4.

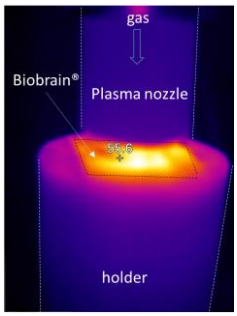

Figure 4. Thermal image of skin udner plasma exposure of 1 min at flow rate of 4 slm and RF power of 15 W with hot spot indication of 55.6 ^{0}C.

Presence of surface/plasma interface drastically change gas flow dynamics and leads to higher temperature of the surface in regards to situation of effluent propagation in the ambient air. This effect is stronger at lower flow rates and higher RF power. At 2 slm gas flow it apparently can lead to surface damage due to high thermal flux to the surface. However, such a negative drawback of plasma treatment can be overcome by application of aerosol injection in the plasma effluent. To this end two types of solutions (without addition of a drug) where studied for aerosol generation: water and ethanol. It was found that flow of aerosol can be used to precisely control temperature of the substrate and insure safe operation of plasma source for a long treatment time of 5-10 minutes without any detectable thermal damage of Biobrain® skin simulation material.

4.Conclusions

The radio-frequency atmospheric pressure plasma source combined with aerosol injection was characterized by the meaning of electrical and plasma diagnostics. Plasma source was designed for topical skin drug delivery. It is revealed based on electrical characterization and RF imaging that the discharge is a capacitive coupled RF plasma operating in diffuse α mode at RF power below 30 W. Phase resolved imaging shows that the bulk plasma between the electrodes is limited by the sheath regions of approximately 200 μm thickness located nearby the electrodes. One of the key parameters, gas temperature, is determined based on emission spectroscopy and validated by two other independent techniques based on laser scattering. Rayleigh scattering has shown uniform temperature distribution in the effluent and it is in a good agreement with OH rotational temperature determined by emission spectroscopy.

It is found that presence of artificial skin material in direct contact with the effluent has a drastic impact on heat distribution in the afterglow. It can lead to heat damage of the substrate even when gas temperature in the effluent is below 50^0 C. It is shown that injection of an aerosol of water or ethanol in the effluent results in a drop of the substrate temperature below a critical point of substrate damage. The method can be used for precise control of the skin heating induced by the discharge in biomedical applications and also for transepidermal delivery of drugs enhanced by direct interaction of plasma activated media with skin surface.

5.Acknowledgements

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6.References

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